# Chlorofluoroacetic Acid Derivatives of Sterically Hindered Chiral Alcohols

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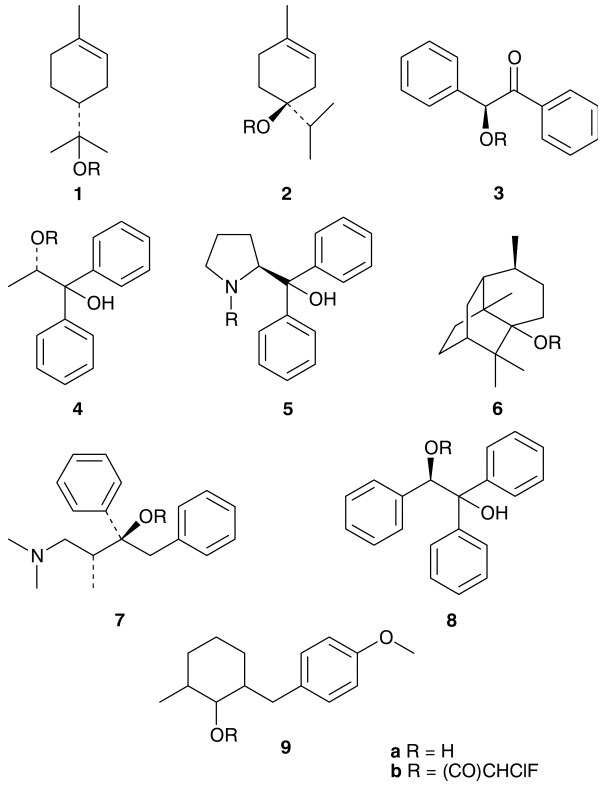
**Josef Růžička,[a] Ludvík Streinz,*[b] Zdeněk Wimmer,[b] Martin Rejzek,[b] Marie Zarevúcka,[b] Bohumír Koutek[b] and Ladislav Lešetický[a]**

[a]*Department of Organic Chemistry, Charles University, 12000 Prague 2, Czech Republic*
[b]*Institute of Organic Chemistry and Biochemistry, 166 10 Prague 6, Czech Republic*

(*R*)- and (*S*)-chlorofluoroacetic acids were found to be an alternative to the Mosher's acid especially when it fails to esterify alcohols from steric reasons.

One of the possible approaches how to determine optical purity is the derivatization of the compound investigated to form diastereoisomers which may be either separated by chromatography or analysed by spectral techniques. The predominant method in this field seems to be the derivatization with Mosher's acid (MPTA). On the other hand, there are examples when this method failed, mainly due to the steric reasons.[3] We have recently offered an alternative to the Mosher's method using both (*R*)- and (*S*)-chlorofluoroacetic acids (CFA) for the derivatization of chiral alcohols demonstrating some advantages of a new method over those used until now.[7] The encouraging results together with the fact that (*R*)- and (*S*)-CFA, as well as the corresponding acid chlorides can be easily prepared,[8–11] prompted us to apply this method on chiral alcohols which are not esterified by the Mosher's acid because of steric reasons. For this purpose, the secondary and tertiary alcohols **1a**–**9a** were selected as models for the reaction with (*R*)- and (*S*)-CFA.




In order to obtain a quantitative esterification with respect to the starting alcohol, we used the 1,3-dicyclohexylcarbodiimide (DCC) method which is known to give esters with sterically hindered alcohols[12,13] and threefold excess of all reagents.[14]

Concerning the reactivity of the model substrates **1a**–**9a**, two trends were apparent. First, the alcohols **1a**, **3a**–**5a** and **7a**–**9a** could be easily converted into the corresponding CFA esters **1b**, **3b**–**5b** and **7b**–**9b**, while the alcohols **2a** and **6a** remained intact, being fully recovered. Secondly, in bifunctional compounds **4a**, **5a** and **8a**, only the secondary alcohol group in **4a** and **8a** was esterified, while the proline derivative **5a** gave the amide **5b**. Although **1a** is unable to afford diastereoisomers separable on silica gel, it was included into the series to demonstrate the capability of CFA to esterify sterically hindered substrates. From similar reasons, the alcohol **9a** as a mixture of (1*R*,2*R*,6*R*)- and (1*S*,2*S*,6*S*)-isomers has been included without determining the configuration on chiral centres.

The CHFCl proton resonance of particular diastereoisomers appearing in $^1$H NMR spectra as a characteristic sharp doublet ($J_{H,F}$ 50 Hz) at $\delta$ 6.13–6.37 represents a favourable feature of the CFA esters facilitating their easy determination.

Some of the CFA diastereoisomers, *i.e.* **4b**, **5b** and **8b**, are well separable on HPLC silica gel, the best resolution showing the amide **5b** ($R_s = 14.2$; TLC: $\Delta R_f = 0.09$). With the exception of the diastereoisomeric esters **7b** and **8b**, as well as amides **5b**, all other diastereoisomers are separable by GC under relatively mild conditions.

Techniques used: $^1$H NMR, HPLC, GLC

References: 17

Tables: 2 (complete IR, mass and $^1$H NMR data as well as chemical shift non-equivalences ($\Delta\delta_H$) and differences in retention times ($\Delta t_r$) of respective diastereoisomers are presented)

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*To receive any correspondence.